PROTOCOL REGISTRATION MANUAL

Office for Policy in Clinical Research Operations
Division of AIDS

DRAFT
November 2009 VERSION

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PROTOCOL REGISTRATION MANUAL

I. INTRODUCTION

The Division of AIDS (DAIDS) Office for Policy in Clinical Research Operations (OPCRO) has established a protocol registration process to ensure that all clinical research sites (CRSs) conducting DAIDS supported and/or sponsored clinical research do so in accordance with DAIDS Policies and Standard Operating Procedures (http://www3.niaid.nih.gov/research/resources/DAIDSClinRsrch/Regulatory.htm) in addition to all applicable regulations for human subjects protection and the use of investigational drugs, biologics and/or devices.

The DAIDS protocol registration process verifies that CRSs have received the necessary Institutional Review Board (IRB)/Ethics Committee (EC) and other applicable regulatory entity (RE) approvals and have provided to DAIDS all documentation pertaining to investigator qualifications and responsibilities that are required by the U.S. federal regulations and the National Institutes of Health (NIH). The DAIDS protocol registration process also verifies that site-specific informed consent forms contain the necessary information to comply with U.S. federal regulations. This includes the basic and additional informed consent form elements as required by U.S. federal regulations at 45 CFR §46[1] and 21 CFR §50[2].

The DAIDS Protocol Registration Manual is a reference tool for CRSs to help them successfully complete the DAIDS protocol registration process. This manual provides an explanation of the different types of protocol registration submissions as well as a list of the required documents for each type of submission.

[1] http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm
[2] https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?CFRPart=50

II. DEFINITIONS

Clinical research: Research conducted on human participants or on material or data of human origin identifiable with the source person. Clinical research includes large and small-scale, exploratory, and observational studies. (DAIDS)

Clinical Research Site (CRS): Distinct locations (e.g., hospitals, outpatient clinics, health maintenance organizations, community health centers, private practices, clinics) supported and/or sponsored by NIAID (DAIDS) where qualified professionals conduct clinical research in accordance with good clinical practice (GCP) and applicable regulations. (DAIDS)

Clinical Research Site (CRS) Leader: The onsite senior research scientist responsible for the administrative and scientific components of the CRS. The CRS leader is responsible for overall site activities, including day-to-day operations, performance, and compliance at the site level. (DAIDS)

Clinical trial: A prospective study of human participants designed to answer questions about biomedical or behavioral interventions, e.g., drugs, treatments, devices, or new ways of using known treatments to determine whether they are safe and effective. (NIAID)

Code of Federal Regulations (CFR): Published by the U.S. Office of the Federal Register National Archives and Records Administration, these are detailed procedures for meeting requirements authorized by law:

Title 21: Food and Drugs (covers regulations administered by FDA as authorized by the Food, Drug and Cosmetic Act)

Title 45: Public Welfare (includes regulations administered by OHRP relating to the protection of human subjects). (DAIDS)

Curriculum Vitae (CV): A statement of investigator's qualifications including professional experience accomplishments, educational background, and any publications. This document is required for all initial protocol registrations. (DAIDS)

Division of AIDS (DAIDS): One of six divisions within the National Institute of Allergy and Infectious Diseases. DAIDS is responsible for the management, initiation, and oversight for the clinical trials and research that is sponsored and/or supported by NIAID (DAIDS). (DAIDS)

DAIDS Protocol Registration Checklist: Document required with each submission made through the electronic protocol registration (EPR) to the DAIDS Protocol Registration Office. (DAIDS)

DAIDS Protocol Registration Office (PRO): An office within the DAIDS Regulatory Support Contract (RSC) that receives and processes all protocol registration materials for DAIDS. (DAIDS)

DAIDS Protocol Registration System (DPRS): An internet-based system that allows DAIDS Clinical Research Sites (CRS) to submit Protocol Registration documents to the DAIDS Protocol Registration Office (PRO). (DAIDS)

DAIDS Regulatory Support Contract (RSC): A contract that provides clinical, regulatory and technical support services for DAIDS supported and/or sponsored clinical trials. (DAIDS)

DAIDS-sponsored: DAIDS is responsible for the management (including submission of the Investigational New Drug Application (IND) and Investigational Device Exemption (IDE) Application to FDA, and initiation of the study) and oversight for the trial. (DAIDS)

DAIDS-supported: Clinical research activities would be considered to be supported by NIAID (DAIDS) under one or more of the following circumstances:

1. DAIDS provides direct funding to an institution via a grant, contract or cooperative agreement for the clinical research activities; or indirect funding via a subcontract executed under a DAIDS-supported award to another institution

2. DAIDS provides other tangible support for the clinical research activities which includes, but is not limited to, regulatory support, site monitoring services, study product supply, management and distribution services

3. DAIDS-supported central laboratory or data management center receives from other organizations specimens or data for processing or analysis and the results or analyses, will be used to direct involvement of participants in clinical research activities. (DAIDS)

Electronic Protocol Registration (EPR): An alternate way CRSs can submit registration materials via email to the DAIDS PRO if they encounter problems when trying to submit registration materials through the DPRS. (DAIDS)

Food and Drug Administration (FDA): A public health agency within the United States (U.S.) Department of Health and Human Services. FDA's mission is to promote and protect public health by helping safe and effective products reach the market in a timely way and monitoring products for continued safety after they are in use as authorized by The Federal Food, Drug and Cosmetic Act. (DAIDS)

Form FDA 1572: FDA required document in which clinical investigators agree to conduct the clinical trials according to U.S. federal regulations. The Form FDA 1572 is signed and a copy submitted to the IND sponsor. (DAIDS)

Institutional Biosafety Committee (IBC): Committee set up by an institution under NIH guidelines to review recombinant DNA research and ensure its appropriate use. IBCs may also review other biohazardous research, including select agents. (NIAID)

Institutional Review Board/Ethics Committee (IRB/EC): A board, committee, or other group formally designated to review, approve, and to conduct periodic review of research involving human participants. The primary purpose of such review is to assure the protection of the rights and welfare of participants in research. (DAIDS)

Investigational New Drug Application (IND): A request for authorization from the FDA to administer an investigational drug or biological product to humans. Such

authorization must be secured prior to interstate shipment and administration of any new drug or biological product that is not the subject of an approved New Drug Application or Biologics/Product License Application. (FDA) An IND application is required by the FDA before clinical trials of an investigational drug or biological agent may be initiated. An IND is also generally required if the U.S. FDA has not approved the route of administration, dosage level, or patient population for the drug or biological agent. (DAIDS)

Investigator of Record (IoR): The individual at the CRS responsible for ensuring that a clinical trial is conducted in accordance with the protocol, applicable U.S. federal regulations, in-country regulations and any provisions imposed by the reviewing IRB/EC/other regulatory entity. This person is the signatory for the Form FDA 1572 for studies conducted under an IND or the DAIDS Investigator of Record Agreement for non-IND studies.

Investigator of Record (IoR) Agreement: A document required by DAIDS for non-IND studies. The IoR is required to sign this document accepting full responsibility for conduct of the trial at their CRS. (DAIDS)

Letter of Amendment (LoA) - A revision to a protocol made by the Protocol Team/Chair/Awardee through a short letter that requires DAIDS final approval/sign-off before implementation. Changes described in a LoA are listed in a document which is separate from the protocol document itself and will NOT result in the change to the DAIDS protocol version number. (DAIDS)

National Institute of Allergy and Infectious Diseases (NIAID): NIH institute that conducts and supports research to understand, treat, and prevent infectious, immunologic, and allergic diseases. (NIAID)

National Institutes of Health (NIH): A Federal agency whose mission is to improve the health of the people of the United States. NIH is a part of the Public Health Service, which is part of the U.S. Department of Health and Human Services. (NIH)

Observational Study: A type of study in which individuals are observed or certain outcomes are measured, but no treatments or interventions are assigned by the study. (DAIDS)

Office for Human Research Protections (OHRP): HHS office overseeing human subject protection for HHS-supported research. (NIH)

Office for Policy in Clinical Research Operations (OPCRO): An office in DAIDS that provides a variety of clinical research management resources and oversight to the DAIDS clinical research portfolio. This includes overseeing the development, standardization, implementation and execution of policies, procedures and standards of conduct for all of DAIDS domestic and international clinical research. (DAIDS)

Protocol registration notifications: The following are notifications that a CRS may receive from the DAIDS PRO:

1. Confirmation of Submission - A notification sent out to the CRS Coordinator and IoR confirming that registration materials have been successfully submitted to the DAIDS PRO. If a CRS does not receive a Confirmation of Submission Notification within 24 hours of submitting registration documents

to the DAIDS PRO, the CRS should contact the DAIDS PRO to find out how to proceed.

2. Registration Notification - A final notification from the DAIDS PRO indicating that a CRS has successfully completed the protocol registration process. If a CRS receives a Registration Notification with Required Corrections, a CRS must make the required corrections and submit them to their IRB/EC for review and approval *OR* must submit justification for why the required correction will not be made within 120 calendar days of the date the Registration Notification with Required Corrections was issued. A Registration Notification with Required Corrections indicates that a CRS may begin using the site-specific ICFs after protocol activation by the appropriate Operations Center, Data Management/Statistical Center or DAIDS Program.
3. Disapproval Notification - A notification from the DAIDS PRO indicating that the site-specific informed consent forms (ICFs) do not include all the required basic and additional elements to comply with U.S. federal regulations and DAIDS policy. The Disapproval Notification will outline the deficiencies that must be revised/corrected before a final Registration Notification can be issued. All revised site-specific ICFs must be approved by the IRB/EC prior to submission to the DAIDS PRO. A disapproval notification is *NOT* a final notification since corrective materials must be resubmitted.
4. Deregistration Notification - A notification from the DAIDS PRO indicating that a CRS is no longer registered to a study and all associated sub-studies.
5. Change of IoR Approval Notification - A notification from the DAIDS PRO indicating that DAIDS has approved the change of IoR for a protocol at a CRS. (DAIDS)

Protocol Registration Team (PRT): A team within OPCRO responsible for managing the Protocol Registration (PR) system, which includes oversight of the DAIDS PRO. (DAIDS)

Regulatory Entity (RE) - Any group other than the local IRB/EC responsible for reviewing and approving a clinical research protocol and site-specific ICFs prior to implementation at a site. For example, in some states within the U.S., institutional approvals are required since these states have research regulations in addition to the federal human subjects protection regulations detailed in U.S. federal regulations (45 CFR §46). In addition, at many non-U.S. sites, several regulatory agency approvals may be required in addition to the local IRB/EC approval which include but are not limited to approvals from ministry of health, national regulatory agency, in-country drug control council, national IRB/EC, or other government agency). (DAIDS)

Sub-Investigator: Any member of the clinical research team designated and supervised by the CRS Leader/IoR of a protocol at a CRS to perform critical trial related procedures and/or to make important clinical trial related decisions. (DAIDS)

III. DAIDS PROTOCOL REGISTRATION OFFICE CONTACT INFORMATION

The DAIDS Protocol Registration Office (PRO) has two different e-mail addresses: one for submission of protocol registration documents and a second for questions and general correspondence.

Contact Information for Questions and General Correspondence:

EMAIL: protocol@tech-res.com

PHONE: 301-897-1707

OFFICE HOURS: Monday through Friday 8:30 AM to 5:00 PM
(U.S. Eastern Standard Time)

Starting May 1, 2010, DAIDS network CRSs are required to submit protocol registration materials to the DAIDS PRO through the DAIDS Protocol Registration System (DPRS). Information on the DPRS and how to request a user name and password is available at http://rcc.tech-res.com/prs/default.html. For information on how to submit protocol registration materials through the DPRS once a CRS has received a user Name and password, refer to Appendix A of this manual.

If a CRS encounters problems when submitting protocol registration materials through the DPRS, a CRS can submit protocol registration materials via e-mail to the DAIDS Electronic Protocol Registration (EPR) mailbox at EPR@tech-res.com. The DAIDS Protocol Registration Checklist must accompany EVERY submission made to the DAIDS PRO through the EPR mailbox. The checklist enables the DAIDS PRO to correctly identify the contents of the submission. Documents submitted for review through the EPR mailbox without a checklist cannot be processed.

NOTE: If protocol registration materials are submitted to the DAIDS PRO through the DPRS, the DAIDS Protocol Registration Checklist is NOT required.

IV. PROTOCOL REGISTRATION REQUIRED DOCUMENTS

DAIDS reviews and approves the final version of each protocol and Sample Informed Consent (SIC) before distribution to the CRSs. CRSs are required to submit the initial version and all subsequent versions of a DAIDS-supported and/or sponsored protocol, including the SIC and site-specific ICFs, to their local IRB/EC and other applicable regulatory entity(ies) for review and approval.

Prior to implementing the protocol and enrolling participants, a CRS must receive approval from their IRB/EC and other applicable regulatory entity(ies). In addition, the CRS must successfully complete the DAIDS protocol registration process. However, a Registration Notification from the DAIDS PRO *DOES NOT* authorize a CRS to begin enrollment of participants. CRSs will be notified by the appropriate DAIDS scientific program (i.e., Program/Project Officer), Operations Center or Data Management Center when enrollment may begin.

Detailed information on specific requirements for each required document for protocol registration is included in sub-sections A-E of this section of the manual. Refer to Section VI – “Protocol Registration Submissions” for more information on the different types of submissions that can be made to the DAIDS PRO.

NOTE: Failure to include any required documents for protocol registration at the time of submission to the DAIDS PRO will result in processing delays until all the required documents are received.

A. FORM FDA 1572

REQUIRED FOR ALL INITIAL REGISTRATIONS FOR STUDIES BEING CONDUCTED UNDER AN IND APPLICATION, WHEN THERE IS ANY CHANGE IN INFORMATION ORIGINALLY SUBMITTED OR WHEN THERE IS A CHANGE OF IoR

A signed Form FDA 1572 is required for each investigator that participates in any clinical trial (drug or biologic) that is conducted under an Investigational New Drug (IND) Application filed with the U.S. FDA. By signing the Form FDA 1572, the Investigator of Record (IoR) affirms that he/she will conduct the clinical trial according to the research protocol and all applicable U.S. federal regulations.

All CRSs participating in a clinical trial conducted under an IND must submit a copy of the signed and dated Form FDA 1572 to the DAIDS PRO as part of the protocol registration submission for review and for submission to the U.S. FDA.

NOTE: CRSs are required to retain the original signed Form FDA 1572 in their regulatory files at the site. Original Form FDA 1572s should not be sent to the DAIDS PRO. If a site submits an original Form FDA 1572 to the DAIDS PRO, the form will copied and the original will be returned to the site.

CRSs requiring more space than what is provided on the Form FDA 1572 can use a supplemental page. The supplemental page provides additional space to document: additional research locations and addresses; laboratory facilities and addresses; and the names of additional sub-investigators. If used, a copy of the supplemental page must also be sent to the DAIDS PRO as part of the protocol registration submission.

A CRS must update and submit a revised copy of the Form FDA 1572 when there is *ANY* change to the information originally submitted to the DAIDS PRO. Any correction or revision requires the IoR to sign and date the newly revised form. CRSs must submit *BOTH* pages (and supplemental page, if applicable) of the revised Form FDA 1572 to the DAIDS PRO even if the changes only affect one page of the form.

NOTE: An updated Form FDA 1572 that is dated the same as the original or previous version will not be accepted.

The most current version of the Form FDA 1572 is available for download on the RSC Web site (http://rcc.tech-res.com) under the “Protocol Registration” section or from the U.S. FDA website (www.fda.gov).

How to complete the Form FDA 1572

The Form FDA 1572 is comprised of 11 sections, 10 of which require data entry. Below is detailed information to assist the CRS in completing the Form FDA 1572.

Section 1 - Name and Address of Investigator of Record (IoR)

This section must contain the complete name and address of the IoR at the CRS that is responsible for the conduct of the clinical trial. The complete legal name of the IoR and the IoR's complete office address (complete physical location/street address) should be included in Section 1. Non-U.S. CRSs should include the complete physical address, including the country.

If a CRS has more than one IoR sharing responsibilities for a clinical trial being conducted under an IND, the CRS must submit a separate Form FDA 1572 for each IoR that is responsible for the clinical trial at that site. The CRS must also submit a memo stating that the two investigators listed in section 1 of each of the Form FDA 1572s are sharing equal responsibilities for the conduct of the clinical trial at the CRS.

Section 2 - Education and Training

This section requires the IoR to check the appropriate box on how they plan to verify their education, training and experience that qualifies them as an expert in the clinical investigation of the study product (drug or biologic) being tested. The box marked "Curriculum Vitae" should be checked and a copy of the IoR's CV must be included in the registration packet that is submitted to the DAIDS PRO. DAIDS does not require the submission of CVs for sub-investigators. All CVs must be submitted in English.

Section 3 - Name and Address of Location(s) Where the Study Will be Conducted

This section must list the name and address of all locations where the clinical trial will be conducted. The complete name and physical address of the CRS (medical school, hospital, or research facility) where the clinical trial will be conducted should be listed in Section 3. This includes facilities where participants will be seen and study procedures performed.

If a CRS utilizes a pharmacy that is directly affiliated with their research institute, it is not necessary to list the pharmacy. If a CRS out-sources the pharmacy responsibilities for the clinical trial, the CRS must list the name and complete physical address of the contracted pharmacy in Section 3.

If an IoR is conducting the same research protocol at more than one CRS overseen by the same IRB/EC, then it is acceptable to submit one Form FDA

1572 which lists all locations where the clinical trial will be conducted. A separate Form FDA 1572 must be submitted for each CRS that has a different IoR and IRB/EC. If more than one CRS is included in Item 3, include the DAIDS site ID for each CRS. Non-U.S. CRSs should include the country in addition to the complete physical address.

Section 4 - Name and Address of Clinical Laboratory

This section must list the name(s) and complete physical address of ALL clinical laboratories or testing facilities that will be used for the clinical trial to process study related and/or study defined samples that will directly contribute to or support the clinical trial. The official name of the laboratory (i.e., Department of Pathology) should be included. If multiple CRSs and/or locations are listed on the Form FDA 1572, the corresponding clinical laboratories must be listed for each CRS and/or location. If a central laboratory is sending samples to its own satellite labs for additional testing, the satellite labs do not need to be listed as long as the central laboratory can trace the samples to the satellite labs where the tests were performed.

Section 5 - Institutional Review Board (IRB)/Ethics Committee (EC) and All Other Regulatory Entity(ies) (RE)

This section must list the name and address of all IRBs, ECs and other applicable REs that are responsible for the review and approval of clinical trials at a CRS prior to the CRS's initiation of the protocol. The official name (refer to the title provided on the IRB/EC and other applicable RE approval letter(s)) and complete physical address of the IRBs/ECs and other applicable REs which reviewed the protocol should be included in Section 5. IRBs/ECs reviewing and approving the clinical trial do not have to be at the same location as the research being conducted.

NOTE: The DAIDS PRO must receive an approval letter for each entity listed in section 5 of the Form FDA 1572. If the other RE is not responsible for the review and approval of full version amendments, LoAs or changes to the CRS's site-specific ICF(s), the CRS Leader or IoR should document this fact in a memo to the DAIDS PRO or in the comments section of the IRB/EC/RE approval field in the DPRS when submitting registration materials.

Section 6 - Names of Sub-Investigators

This section must list the names of all study staff at a CRS that are responsible for making a "direct and significant contribution to the data." A direct and significant contribution includes any persons directly responsible for the treatment or evaluation of research participants.

Hospital staff, including nurses, residents, fellows, and office staff who provide ancillary or intermittent care but who do not make a direct and significant contribution to the data do not need to be listed. It is not necessary to include in Section 6 a person with only an occasional role in the conduct of the research, e.g. an on-call physician who temporarily dealt with a possible adverse event or a temporary substitute for any research staff. If a number of residents on rotation will participate in the clinical trial, a general statement regarding their planned participation may be included in Section 6.

If a pharmacist is merely dispensing tablets and has no responsibility for preparing the test article(s) or evaluating or reporting data relative to the study activities, then it is not necessary to list the pharmacist. On the other hand, if the pharmacist will be compounding, labeling, monitoring or reporting test article compliance data, it would be appropriate to list the pharmacist in Section 6.

CRSs are required to list, at a minimum, one sub-investigator who will be responsible for fulfilling the requirements of the IoR should the IoR not be able to meet his/her requirement for any given reason. The complete name(s) of the sub-investigators who will assist the IoR in the conduct of the protocol should be listed in Section 6.

The IoR is responsible for determining the sub-investigators to be included on the Form FDA 1572. Individuals who will sign study medication prescriptions and physicians who submit SAE/EAEs to DAIDS must be listed on the Form FDA 1572. The IoR must designate a physician as a sub-investigator who will be responsible for backing up the IoR.

NOTE: Any physician that is responsible for the review and submission of SAE/EAEs to DAIDS must be listed in Section 6 of the Form FDA 1572. Safety reports cannot be submitted by a physician that is not listed in section 6 of the Form FDA 1572.

NOTE: CRSs must list the CRS Leader as a Sub-investigator in Section 6 on all Form FDA 1572s if the IoR for the protocol, listed in Item # 1, is not the CRS Leader. If the CRS Leader is the same person listed in Item # 1 on the Form FDA 1572 (Protocol IoR) then the CRS Leader does NOT need to be listed again as a Sub-investigator.

NOTE: CRS Leaders are responsible for making sure that a financial disclosure form is completed and submitted to their appropriate Network Operations Center for each individual listed in Sections 1 and 6 of the Form FDA 1572. Non-network investigators should submit a financial disclosure form to their DAIDS Program Officer.

Section 7 - Protocol Name and Protocol Number:

The DAIDS/Network protocol ID number and the complete protocol title should be included in Section 7.

NOTE: Short titles cannot be accepted and will result in the CRS having to submit a revised Form FDA 1572 which will delay protocol registration.

CRSs should not include the DAIDS protocol version number in Section 7. CRSs that include the protocol version number in Section 7 will be required to submit an updated Form FDA 1572 with each full version amendment of the protocol.

Section 8 - Clinical Protocol Information:

As the IND sponsor, DAIDS submits the protocol and all relevant information to the FDA on behalf of investigator. This section should be left blank.

Sections 9, 10 and 11:

The IoR must read Section 9, sign Section 10 and date Section 11. The complete legal signature of the IoR should be included in Section 10 and should correspond with the name in Section 1 of the Form FDA 1572.

NOTE: If a CRS must update their Form FDA 1572, the IoR is responsible for signing and dating the new document even if the change(s) only affect page 1. An updated Form FDA 1572 that is dated the same as the original or previous version will not be accepted.

B. DAIDS INVESTIGATOR of RECORD AGREEMENT (IoR)

SHOULD BE SUBMITTED FOR INITIAL REGISTRATION FOR STUDIES NOT BEING CONDUCTED UNDER AN IND APPLICATION, WHEN THERE IS ANY CHANGE IN INFORMATION ORIGINALLY SUBMITTED OR WHEN THERE IS A CHANGE OF IOR

A signed DAIDS IoR Agreement should be submitted for each investigator that participates in a clinical trial that is sponsored and/or supported by DAIDS and is NOT conducted under an IND filed with the U.S. FDA. By signing the DAIDS IoR Agreement, the Investigator of Record (IoR) affirms that he/she will conduct the clinical trial according to the research protocol and all applicable U.S. federal regulations and DAIDS requirements/policies.

The IoR agreement contains the same information as the Form FDA 1572 without the legal language that pertains only to studies conducted under an IND.

All CRSs must submit a copy of the signed and dated DAIDS IoR Agreement to the DAIDS PRO as part of the protocol registration submission for review.

NOTE: CRSs are required to retain the original signed IoR Agreement in their regulatory files at the site. Original IoR Agreements should not be sent to the DAIDS PRO. If a site submits an original IoR Agreement to the DAIDS PRO, the form will be copied and the original returned to the site.

CRSs requiring more space than what is provided on the Form FDA 1572 can use a supplemental page. The supplemental page provides additional space to document: additional research locations and addresses; laboratory facilities and addresses; and the names of additional sub-investigators. If used, a copy of the supplemental page must also be sent to the DAIDS PRO as part of the initial protocol registration submission.

A CRS should update and submit a revised copy of the DAIDS IoR Agreement when there is *ANY* change to the information originally submitted to the DAIDS PRO. Any correction or revision requires the IoR to sign and date the newly revised form. CRSs must submit *BOTH* pages (and supplemental page, if applicable) of the revised DAIDS IoR Agreement to the DAIDS PRO even if the changes only affect one page of the form.

NOTE: An updated DAIDS IoR Agreement that is dated the same as the original or previous version will not be accepted.

The most current version of the DAIDS IoR Agreement is available for download on the RSC Web site (http://rcc.tech-res.com) under the "Protocol Registration" section.

How to complete the DAIDS IoR Agreement:

The DAIDS IoR Agreement is comprised of 10 sections, 9 of which require data entry. Listed below is detailed information to assist the CRS in completing the DAIDS IoR Agreement.

Section 1 - Name and Address of Investigator of Record (IoR)

This section must contain the complete name and address of the IoR at the CRS that is responsible for the conduct of the clinical trial. The complete legal name of the IoR and the IoR's complete office address (complete physical location/street address) should be included in Section 1. Non-U.S. CRSs should include the complete physical address, including the country.

If a CRS has more than one IoR sharing responsibilities for a Non-IND study, the CRS must submit a separate DAIDS IoR Agreement for each IoR that is responsible for the study at that site. The CRS must also submit a memo stating that the two investigators listed in Section 1 of each of the DAIDS IoR Agreements are sharing equal responsibilities for the conduct of the study at the CRS.

Section 2 – Education, Training, and Experience

This section requires the IoRs to check the appropriate box regarding how they plan to verify that their education, training and experience qualifies them as an expert in the clinical investigation of the study product (drug or biologic) being tested. The box marked "Curriculum Vitae" should be checked and a copy of the IoR's CV must be included in the registration packet that is submitted to the DAIDS PRO. DAIDS does not require the submission of CVs for sub-investigators. All CVs must be submitted in English.

Section 3 – Name, Address, and DAIDS CRS ID Number of Location(s) Where the Study Will be Conducted

This section must list the name and address of all locations where the clinical trial will be conducted. The complete name and physical address of the CRS (medical school, hospital, or research facility) where the clinical trial will be conducted should be listed in Section 3. This includes facilities where participants will be seen and study procedures performed.

If a CRS utilizes a pharmacy that is directly affiliated with their research institute, it is not necessary to list the pharmacy on the DAIDS IoR Agreement. If a CRS out-sources the pharmacy responsibilities for the clinical trial the CRS must list the name and complete physical address of the contracted pharmacy in Section 3.

If an IoR is conducting the same research protocol at more than one CRS overseen by the same IRB/EC, then it is acceptable to submit one DAIDS IoR Agreement which lists all locations where the clinical trial will be conducted. A separate DAIDS IoR Agreement must be submitted for each CRS that has a different IoR and IRB/EC. If more than one CRS is included in Item 3, include the DAIDS site ID for each CRS. Non-U.S. CRSs should include the country in addition to the complete physical address.

Section 4 - Name and Address of Clinical Laboratory

This section must list the name(s) and complete physical address location of ALL clinical laboratories or testing facilities that will be used for the clinical trial to process study related and/or study defined samples that will directly contribute to or support the clinical trial. The official name of the laboratory (i.e., Department of

Pathology) should be included. If multiple CRSs and/or locations are listed on the DAIDS IoR Agreement, the corresponding clinical laboratories must be listed for each CRS and/or location. If a central laboratory is sending samples to its own satellite labs for additional testing, the satellite labs do not need to be listed as long as the central laboratory can trace the samples to the satellite labs where the tests were performed.

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NOTE: The DAIDS PRO must receive an approval letter for each entity listed in Section 5 of the IoR Agreement. If the other RE is not responsible for the review and approval of full version amendments, LoAs or changes to the CRS's site-specific ICF(s), the CRS Leader or IoR should document this fact in a memo to the DAIDS PRO or in the comments section of the IRB/EC/RE approval field in the DPRS when submitting registration materials.

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If a pharmacist is merely dispensing tablets and has no responsibility for preparing the test article(s) or evaluating or reporting data relative to the study activities, then it is not necessary to list the pharmacist. On the other hand, if the pharmacist will be compounding, labeling, monitoring or reporting test article compliance data, it would be appropriate to list the pharmacist in Section 6.

CRSs are required to list at minimum, one sub-investigator who will be responsible for fulfilling the requirements of the IoR should the IoR not be able to meet his/her requirement for any given reason. The complete name(s) of the sub-investigators who will assist the IoR in the conduct of the protocol should be listed in Section 6.

The IoR is responsible for determining the sub-investigators to be included on the DAIDS IoR Agreement. Individuals who will sign study medication prescriptions and physicians who submit SAE/EAEs to DAIDS must be listed on the DAIDS IoR Agreement. The IoR must designate a physician as a sub-investigator that will be responsible for backing up the IoR.

NOTE: Any physician that is responsible for the review and submission of SAE/EAEs to DAIDS must be listed in Section 6 of the DAIDS IoR Agreement. Safety reports cannot be submitted by a physician that is not listed in Section 6 of the IoR Agreement.

NOTE: CRSs must list the CRS Leader as a Sub-investigator in Section 6 on all IoR Agreements if the IoR for the protocol, listed in Item # 1, is not the CRS Leader. If the CRS Leader is the same person listed in Item # 1 on the DAIDS IoR Agreement (Protocol IoR) then the CRS Leader does NOT need to be listed again as a Sub-investigator.

Section 7 - Study Title and Protocol ID Number:

The DAIDS/Network protocol ID number and the complete protocol title should be included in Section 7.

NOTE: Short titles cannot be accepted and will result in the CRS having to submit a revised DAIDS IoR Agreement which will delay protocol registration.

CRSs should not include the protocol version number in Section 7. CRSs that include the protocol version number in Section 7 will be required to submit an updated IoR Agreement with each full version amendment of the protocol.

Sections 8, 9, and 10:

The IoR must read Section 8, sign Section 9 and date Section 10. The complete legal signature of the IoR should be included in Section 9 and should correspond with the name in Section 1 of the DAIDS IoR Agreement.

NOTE: If a CRS must update their DAIDS IoR Agreement, the IoR is responsible for signing and dating the new document even if the change(s) only affect page 1. An updated DAIDS IoR Agreement that is dated the same as the original or previous version will not be accepted.

C. CURRICULUM VITAE (CV)

REQUIRED FOR ALL INITIAL REGISTRATIONS AND WHEN THERE IS ANY CHANGE IN INFORMATION ORIGINALLY SUBMITTED OR A CHANGE OF IoR

The Investigator of Record (IoR) overseeing DAIDS-supported and/or sponsored clinical research must provide evidence of qualifications (experience, training and education) to assume responsibility for the conduct of clinical trials. CRSs must submit to the DAIDS PRO, a CV for the IoR for all initial protocol registrations. All CVs must provide sufficient documentation for DAIDS to verify the IoR(s) qualifications to conduct a clinical trial.

All investigators must sign and date their CV prior to submission to the DAIDS PRO. An updated CV must be submitted to the DAIDS PRO when there is a *major* change in education, affiliation or responsibilities of the IoR. All IoRs are required to submit a newly signed and dated CV at a minimum of every 2 years.

U.S. federal regulations require that the IoR's CV be submitted to the U.S. FDA for all studies being conducted under an IND. DAIDS, as the IND sponsor, submits the IoR CV to the U.S. FDA. Sub-investigators are not required to submit CVs to the DAIDS PRO.

DAIDS accepts a NIH BioSketch formatted CV that includes education/training, current employment, past relevant employment, licensures/memberships, and any relevant publications.

D. DOCUMENTATION OF INSTITUTIONAL REVIEW BOARD/ETHICS COMMITTEE (IRB/EC) & OTHER REGULATORY ENTITY (RE) APPROVALS

REQUIRED FOR ALL INITIAL, AMENDMENT and LoA REGISTRATIONS, CONTINUING/ANNUAL REVIEW SUBMISSIONS, SITE INITIATED REVISIONS TO SITE-SPECIFIC ICFs, ADMINSTRATIVE REGISTRATIONS, AND SUBMISSION OF REVISED SITE ICF(s) IN RESPONSE TO A DISAPPROVAL NOTIFICATION

i. IRB/EC Approvals:

CRSs are required to submit the most current version and all subsequent versions of DAIDS-supported and/or sponsored clinical trials and observational studies, including the sample informed consent (SIC) and site-specific ICFs, to their IRB/EC and other applicable RE(s) for review and approval. CRSs must submit a copy of *ALL* correspondence to and from the IRB/EC along with a copy of the final approval letter(s) to the DAIDS PRO as part of the protocol registration submission. Original documents should be kept in the regulatory files at the CRS. The IRB/EC approval letter(s) accompanying all initial, amendment and LoA registrations must be a final approval not requiring any modifications to the site-specific ICF(s).

All IRB/EC approval letter(s) must be able to be linked to the most current DAIDS-approved version of the protocol. If an IRB/EC does not include the DAIDS required identifying information in their approval letters, CRSs can submit a memo with their IRB/EC submission which includes identifying information for the protocol, lists all the documents submitted for IRB/EC review as well as the date of submission to the IRB/EC. The required identifying information is:

- Complete Protocol Title for the current DAIDS-approved version of the protocol. The DAIDS PRO will accept a long or short title for those protocols that include both on the DAIDS sample informed consent forms.
- DAIDS and/or Network Protocol ID Number
- DAIDS Protocol Version Number from the final version of the protocol approved by DAIDS *AND/OR* the final version date of the protocol document approved by DAIDS.

The CRS's memo can be used to document that the IRB/EC received the correct version of the protocol and should be included with the IRB/EC approval letters that are submitted to the DAIDS PRO.

NOTE: The CRS's memo to the IRB/EC requesting review must pre-date the date on the final IRB/EC approval letter(s).

NOTE: If any of the IRB/EC approval letter(s) or CRS's memo do not contain enough information to be linked to the most current DAIDS-approved version of the protocol, designated site personnel (i.e., CRS coordinator, IoR) and/or additional personnel listed in the DPRS will be sent a Materials Request notice that details the missing and/or corrected information/materials that must be submitted to the DAIDS PRO for registration processing to continue. The review process will not continue until the requested materials are received at the DAIDS PRO. For information on how to submit requested materials refer to Section VI, Sub Section C.iv.- "Requested Materials" of this manual.

ii. Other RE Approvals

When other RE approvals are required at a CRS, copies of the approval letter for each RE must be submitted to the DAIDS PRO with registration materials.

NOTE - If a given RE requires submission of initial versions of protocols but does not review and approve full version amendments and LoAs, the CRS Leader or IoR should document this fact in the comments section of the IRB/EC/RE approval field in the DPRS or with a memo to the DAIDS PRO when submitting registration materials.

iii. Documentation of Pediatric Risk/Benefit Category

Per the DAIDS Policy for Enrolling Children (including Adolescents) in DAIDS-supported and/or sponsored Human Subject Clinical Research, for research studies including children or adolescents, DAIDS requires documentation of the IRB/EC designation of the pediatric risk/benefit category from the U.S. federal regulations[3] and IRB/EC approval for involvement of children based on the determination specified by that category. This requirement applies to the initial and continuing/annual reviews of research protocols and to any subsequent reviews of full version of LoAs involving potential study risks or benefits. The documentation may be in the IRB/EC approval letter(s) of in other official correspondence from the IRB/EC to the site Investigator.

NOTE: Failure to submit documentation of the IRB/EC designation of the pediatric risk/benefit category or documentation that the CRS will not enroll children or adolescents at the time of registration submission to the DAIDS PRO will result in delays in protocol registration.

[3] 45 CFR §46.404-407 & 21 CFR §50.51-54

iv. Institutional Biosafety Committee (IBC) Approval

REQUIRED FOR ALL INITIAL REGISTRATIONS

Research supported by NIH funding that involves recombinant DNA is subject to special regulatory oversight by and IBC. In addition, clinical trials testing products containing recombinant DNA must be submitted to the NIH Office for Biotechnology Activities (OBA) for review by the NIH Recombinant DNA Advisory Committee (RAC). Detailed information regarding the requirements for DAIDS - sponsored and/or supported research involving recombinant DNA is available on the RCS website (http://rcc.tech-res.com) under the "Protocol Registration" section.

Once IBC approval is received, a copy of the final approval letter must be submitted to the DAIDS PRO with the initial registration submission. Failure to submit documentation of IBC approval at the time of initial registration submission to the DAIDS PRO will result in delays in protocol registration.

All IBC approval letter(s) must be able to be linked to the most current DAIDS-approved version of the protocol at the time of initial protocol registration. Since not all IBCs include the DAIDS-required identifying information in their approval letters, a CRS can submit a memo with their IBC submission which lists identifying information for the protocol, lists all the documents submitted for review as well as the date of submission to the IBC. The required identifying information is:

- Complete Protocol Title for the current DAIDS-approved version of the protocol. The DAIDS PRO will accept a long or short title for those protocols that include both on the DAIDS sample informed consent forms.
- DAIDS and/or Network Protocol ID Number
- DAIDS Protocol Version Number from the final version of the protocol approved by DAIDS *AND/OR* the final version date of the protocol document approved by DAIDS.

The CRS's memo can be used to document that the IBC received the correct version of the protocol and should be included with the IBC approval letter that is submitted to DAIDS PRO.

NOTE: The CRS's memo to the IBC requesting review must pre-date the date on the final IRB/EC approval letter(s).

NOTE: If the IBC approval letter or CRS's memo does not contain enough information to be linked to the most current DAIDS-approved version of the protocol, designated site personnel (i.e., CRS coordinator, IoR) and/or additional personnel listed in the DPRS will be sent a Materials Request notice that details the missing and/or corrected information/materials that must be submitted to the DAIDS PRO for registration processing to continue. The review process will not

continue until the requested materials are received at the DAIDS PRO. For information on how to submit requested materials refer to Section VI, Sub Section C.iv.- "Requested Materials" of this manual.

E. SITE-SPECIFIC INFORMED CONSENT FORMS (ICFs)

REQUIRED FOR ALL INITIAL, AMENDMENT & LoA REGISTRATIONS IF THERE WAS A CHANGE TO THE SITE-SPECIFIC ICFs, CONTINUING/ANNUAL REVIEW SUBMISSIONS IF THERE WAS A CHANGE TO THE SITE-SPECIFIC ICFs, SITE INITIATED REVISIONS TO SITE-SPECIFIC ICFs, & SUBMISSION OF REVISED SITE ICFs IN RESPONSE TO A DISAPPROVAL NOTIFICATION

Site-specific ICF(s) must contain all information necessary to comply with U.S. federal regulations and DAIDS policies. This includes all the basic and additional elements, as appropriate, as outlined in U.S. federal regulations[4]. It is recommended that sites develop their own site-specific ICF(s). To assist sites with developing their site-specific ICF(s), DAIDS works with the Protocol Teams to create sample informed consents (SIC) that contain all the specific elements required by the U.S. federal regulations[5].

A CRS must submit to the DAIDS PRO a copy of all site-specific ICF(s) after review and approval by the IRB/EC and other applicable REs, and retain the original(s) on file at the site.

If some SIC forms provided with the protocol will *not* be needed at a CRS, (e.g. if a pregnancy consent is not needed because pregnant women will not be enrolled), the CRS should document this either in the comments section of the ICF field of the DPRS or with a memo to the DAIDS PRO with the registration submission.

When an IRB/EC approves a site-specific ICF and the site contact information is left blank, the CRS must include a memo with their registration submission explaining that the CRS will insert the site-specific contact information prior to consenting participants.

If a CRS deletes or makes any substantive change to basic and/or additional elements as presented in the SIC, the IoR for the clinical trial must provide documentation to explain the deletions/change(s) at the time of registration submission to the DAIDS PRO.

[4] 45 CFR §46.116 & 21 CFR §50.25
[5] 45 CFR §46.116 & 21 CFR §50.25

All site-specific ICF(s) must be able to be linked to the most current DAIDS approved version of the protocol. The DAIDS-required identifying information is:

- Complete Protocol Title for the current DAIDS-approved version of the protocol. The DAIDS PRO will accept a long or short title for those protocols that include both on the DAIDS sample informed consent forms.
- DAIDS and/or Network Protocol ID Number
- DAIDS Protocol Version Number from the final version of the protocol approved by DAIDS *AND/OR* the final version date of the protocol document approved by DAIDS.

NOTE: For version tracking purposes at the CRS (i.e., at the request of an IRB/EC and other applicable REs), CRSs can specify the site (local) version number or version date of the site-specific ICF(s) in the header or footer of their site-specific ICF(s). However, the DAIDS protocol version number should remain on all site-specific ICFs as well.

NOTE: If any of the site-specific ICFs do not contain enough information to be linked to the most current DAIDS approved version of the protocol, designated site personnel (i.e., CRS coordinator, IoR) and/or additional personnel listed in the DPRS will be sent a Materials Request notice that details the missing and/or corrected information/materials that must be submitted to the DAIDS PRO for registration processing to continue. The review process will not continue until the requested materials are received at the DAIDS PRO. For information on how to submit requested materials refer to Section VI, Sub Section C.iv.- "Requested Materials" of this manual.

Additional guidance is available to assist sites when developing their site-specific ICF(s). This information is located on the RSC web sites (http://rcc.tech-res.com) under the "Protocol Registration" section.

i. Types of ICFs and Protocol Registration requirements

Main ICF: The Main ICF is used for enrollment of participants into the protocol. The Main ICF should include all of the basic and appropriate additional elements as outlined in U.S. federal regulations[6]. The following is a link to OHRP's guidance on informed consent form required elements (www.hhs.gov/ohrp/humansubjects/assurance/consentckls.htm).

Screening ICFs: The following are DAIDS requirements regarding generic screening consent forms and protocol-specific screening consent forms:

[6] 45 CFR §46.116 & 21 CFR §50.25

Generic screening ICF: A generic screening ICF is a screening ICF developed by the CRS and approved by the IRB/EC for use in various clinical research protocols conducted at the CRS. A CRS should NOT submit the site's generic screening ICF to the DAIDS PRO. The DAIDS PRO will NOT review or approve generic screening ICFs.

Protocol-specific screening ICF: A protocol-specific screening ICF is a screening ICF developed for a specific protocol that is approved by DAIDS and is included as part of the final protocol and SICs. If the DAIDS-approved Main ICF includes screening procedures and a CRS chooses to develop a separate protocol-specific screening ICF to be used at the site, then the screening and eligibility information can be removed from the site-specific main ICF. In this instance the CRS must submit *BOTH* the protocol-specific screening ICF and the site-specific main ICF to the DAIDS PRO for review and approval.

Short ICFs: If a CRS elects to use a short ICF in addition to the main ICF, the CRS must have a main ICF *OR* written summary that includes all of the required basic and appropriate additional elements that has been approved by the IRB/EC and other applicable RE and has been submitted to the DAIDS PRO for registration.

Sub-study ICFs: If a DAIDS-supported and/or -sponsored protocol includes a separate ICF for a sub-study that is part of the main protocol and the CRS anticipates participating in the sub-study, the CRS must include the sub-study site-specific ICF in their protocol registration submission. A CRS must receive a Registration Notification from the DAIDS PRO for all sub-study ICFs prior to implementation.

Pregnancy ICF: If a DAIDS- supported and/or sponsored protocol includes a SIC for women who become pregnant while on study and the CRS anticipates that some pregnant women may be included or followed on the study, the CRS must submit the site-specific pregnancy ICF to the DAIDS PRO.

Sites have the flexibility to combine the pregnancy ICF and the main ICF into one ICF, as long as the required information is still present and this approach is approved by the IRB/EC. If one or more ICFs are combined, there should be a note to the DAIDS PRO documenting why one of the original consents is not included in the registration submission.

If the site will not follow or enroll pregnant women, the pregnancy ICF does not need to be submitted, and the site should document the plan not to include pregnant women with a note to the DAIDS PRO. A CRS must receive a Registration Notification from the DAIDS PRO for any pregnancy ICF prior to implementation.

Assents: The IRB/EC must determine that adequate provisions are made for soliciting the assent of children and/or adolescents when in the judgment of the IRB/EC the children and/or adolescents are capable of providing it[7]. The IRB/EC is responsible for determining the age of assent and for determining whether the use of an assent form is appropriate. Assent forms do not need to be submitted to the DAIDS PRO.

ii. Health Insurance Portability and Accountability Act (HIPAA) – Privacy Rule

The Privacy Rule is a U.S. federal regulation under the Health Insurance Portability and Accountability Act (HIPAA) of 1996 that governs the protection of individually identifiable health information.

The DAIDS PRO does not review site ICFs for information related to HIPAA. If the site-specific ICF(s) contains language pertaining to HIPAA authorization, the DAIDS PRO will NOT assess this language for Privacy Rule compliance. In addition, it is very important that confidentiality language included in the DAIDS-approved sample informed consent remain in the site-specific ICF even if this information is included in a separate HIPAA authorization form.

NOTE: Non-U.S. CRSs are not required to follow HIPAA regulations.

Information related to the Privacy Rule can be found at the following website: www.hhs.gov/ocr/hipaa.

[7] 45 CFR §46.408

V. TRANSLATION REQUIREMENTS

For all documents that require translation, a CRS must submit to the DAIDS PRO a copy of the DAIDS Protocol Registration Translation Confirmation Document, attesting that the translation is a true and accurate reflection of the local language documents that have been reviewed and approved by the IRB/EC and other REs.

NOTE –One DAIDS Protocol Registration Translation Confirmation Document is required to attest to the accuracy of the translation for all of the protocol registration documents below.

An electronic copy of the DAIDS Translation Confirmation Document can be found on the DAIDS RSC web site (http://rcc.tech-res.com) under the "Protocol Registration" section.

i. Form FDA 1572, IoR Agreement and CVs:

CRSs are required to submit a copy of all Form FDA 1572s, IoR Agreements and CVs in English. Form FDA 1572s, IoR Agreements and CVs that are received by the DAIDS PRO in a language other than English will not be accepted and the CRS will be required to submit a new Form FDA 1572s, IoR Agreements and CVs in English.

ii. IRB/EC and Other RE approval letters:

All non-English IRB/EC and other applicable RE approval letter(s) must be translated into English, with the exception of Spanish. CRSs must submit copies of both the local language and translated English approval letter(s) to the DAIDS PRO.

iii. Site-specific ICFs:

Back translations are *NOT* required if a CRS has an English site-specific ICF that has been approved by the IRB/EC and other applicable REs. A CRS must submit the English site-specific ICF and all local language site-specific ICF(s) that have been approved by the IRB/EC and other applicable REs to the DAIDS PRO for review.

Back translations *ARE* required if a CRS *ONLY* has local language site-specific ICF(s) that have been approved by the IRB/EC and other applicable REs. A CRS must submit all local language site-specific ICF(s) that have been approved by

the IRB/EC and other applicable REs along with the English back translation(s) to the DAIDS PRO for review.

NOTE: If a DAIDS Clinical Trials Network has specific requirements regarding translation of site-specific ICFs, the CRS should follow those requirements for translation of local language site-specific ICFs.

iv. Spanish Site-specific ICFs:

If a CRS has an English *AND* Spanish site-specific ICF that has been approved by the IRB/EC and other applicable REs the CRS must submit the English *AND* Spanish site-specific ICF(s) to the DAIDS PRO for review.

If a CRS *ONLY* has a Spanish site-specific ICF that has been approved by the IRB/EC and other applicable REs the CRS must submit the Spanish site-specific ICF(s) to the DAIDS PRO for review.

NOTE – An English back translation is not required for Spanish site-specific ICFs.

NOTE – CRS are not required to complete the DAIDS Protocol Registration Translation Confirmation Document for any protocol registration documents in Spanish.

VI. PROTOCOL REGISTRATION SUBMISSIONS

Prior to implementing a protocol and enrolling participants, a CRS must receive final approval for the site-specific ICFs from the IRB/EC and other applicable REs. In addition, the CRS must successfully complete the DAIDS initial protocol registration process. However, successfully completing the DAIDS initial protocol registration process *does not* authorize a CRS to begin enrollment of participants. CRSs will be notified by the appropriate DAIDS scientific program (i.e., Program Officer), Operations Center or Data Management Center when enrollment may begin for a protocol.

Each CRS will complete the protocol registration process for all clinical research supported and/or sponsored by DAIDS. Upon receiving final IRB/EC and other applicable RE approval(s), the CRS will submit all required registration documents to the DAIDS PRO via the DAIDS DPRS.

Upon making *ANY* submission to the DAIDS PRO, a CRS will receive a Confirmation of Submission notice that indicates successful submission of materials to the DAIDS PRO.

The CRS must place a copy of all final Protocol Registration notifications from the DAIDS PRO in the site's regulatory files.

A. INITIAL REGISTRATION

A CRS that has *NEVER* received a Registration Notification from the DAIDS PRO for any version of the protocol must complete the initial protocol registration process. The DAIDS PRO will issue a decision for all initial registration submissions within 10 business days from the date of receipt of a complete packet.

If a CRS has previously received a DAIDS PRO Registration Notification for one language (i.e., English) and later submits registration documents for a new language (i.e., Spanish) , the new language is considered an initial registration as this is the first time the specific language has been submitted to the DAIDS PRO for review.

If a CRS has previously received a Registration Notification from the DAIDS PRO for one informed consent type (i.e., main, pregnancy, etc.) and later submits registration documents for a new informed consent type (i.e., stored specimens), the new informed consent type is considered an initial registration as this is the first time the informed consent form has been submitted to the DAIDS PRO for review.

The following documents must be submitted to the DAIDS PRO for all initial registration submissions:

- A copy of the Form FDA 1572 signed and dated by the IoR (for studies conducted under an IND)

OR

- A copy of the DAIDS IoR Agreement signed and dated by the IoR (for non-IND studies)
- Investigator of Record CV
- A copy of the CRS's IRB/EC and other applicable RE approval letter(s) and any other appropriate documentation/correspondence with the IRB/EC and other applicable REs
- A copy of the IRB/EC and other applicable RE approved site-specific ICFs (all languages including English translations, if applicable)
- A copy of the CRS's IBC approval letter, if applicable

NOTE: If an initial registration submission is missing any required documents or is incomplete, designated site personnel (i.e., CRS coordinator, IoR) and/or additional personnel listed in the DPRS will be sent a Materials Request notice that details the missing and/or corrected information/materials that must be submitted to the DAIDS PRO for registration processing to continue. The review process will not continue until the requested materials are received at the DAIDS PRO. For information on how to submit requested materials refer to Section VI, Sub Section C.iv.- "Requested Materials" of this manual.

A CRS will receive a Registration Notification from the DAIDS PRO that will include all languages and informed consent types that have been submitted. The Registration Notification from the DAIDS PRO indicates successful completion of the initial protocol registration process.

If a CRS receives a Registration Notification with Required Corrections, a CRS must make the required corrections and submit them to their IRB/EC for review and approval OR must submit justification for why the required correction will not be made to the DAIDS PRO within 120 calendar days of the date the Registration Notification with Required Corrections was issued. For information on how to submit required corrections refer to Section VI, Sub Section C.iv.- "Requested Materials" of this manual.

Upon successful completion of the DAIDS PRO initial registration process, a CRS will begin receiving safety information for the protocol (e.g. safety reports, safety memos, investigator's brochures, etc.) from the DAIDS RSC Safety Information Center.

If a site-specific ICF(s) does not include all the required basic and appropriate additional elements to comply with U.S. Federal Regulations and DAIDS policies, designated CRS personnel (i.e., CRS Coordinator, IoR) will be notified via a Disapproval Notification from the DAIDS PRO regarding the deficiencies. The Disapproval Notification will outline the deficiencies in the site-specific ICF(s) that must be revised/corrected before a final Registration Notification can be issued.

NOTE - A Disapproval Notification is not a final notification and DOES NOT indicate successful completion of the protocol registration process.

For information on the options a CRS has upon receipt of a Disapproval Notification from the DAIDS PRO, refer to Section VI, Sub Section C.i.- "Disapprovals" of this manual.

B. AMENDMENT REGISTRATIONS

i. Full Version Protocol Amendment Registration

A full version "Protocol Amendment" is a revision to a protocol made by the Protocol Team/Chair/Awardee that requires DAIDS review and final approval/sign-off before implementation. The changes to the protocol are incorporated into the protocol document and will result in a change to the DAIDS protocol version number (e.g., 2.0, 3.0, etc.).

If a CRS has received a Registration Notification from the DAIDS PRO for an earlier version of the protocol including all informed consent types and specific language(s), then the registration to a new version of the protocol would be a full version protocol amendment. A CRS that has never received a Registration Notification from the DAIDS PRO for any version of the protocol, language or informed consent type must follow the instructions for Initial Protocol Registration detailed in Section VI, sub-section A of this manual.

Per the DAIDS Protocol Registration policy, CRSs are required to submit the amended protocol, SIC(s), and the amended site-specific ICF(s), to their IRB/EC and other applicable REs for review and approval within 30 calendar days for U.S. sites and 60 calendar days for non-U.S. sites of the date the amendment was approved by DAIDS and distributed to the sites.

NOTE: The 30 or 60 calendar day requirement for submission of amendment materials is for local IRB/EC only.

Once a CRS has received final approval from the IRB/EC and other applicable REs, the amended protocol and any revised site-specific ICF(s) must be

implemented immediately. A CRS must submit amendment registration documents to the DAIDS PRO within 14 calendar days of the CRS's receipt of final IRB/EC approval for the amendment. The submitted documents must include documentation of the date the amended protocol and any revised site-specific ICF(s) were submitted to the IRB/EC.

The following documentation must be submitted to the DAIDS PRO for all amendment registration submissions:

- A copy of the site's IRB/EC and other applicable RE approval letter(s) and any other documentation/correspondence with the IRB/EC and other applicable REs
- Documentation of the date the amended protocol and any revised site-specific ICF(s) were submitted to the IRB/EC
- A copy of the IRB/EC and other applicable RE approved site ICF(s) (all languages including English translations, if applicable)

NOTE: If the IRB/EC determines that an amendment does not require changes to the site-specific ICF(s), the CRS should document this either in the comments section of the ICF field of the DPRS or with a memo to the DAIDS PRO with the amendment registration submission. The Registration Notification from the DAIDS PRO will only list the ICFs listed in the comments section of the DPRS in the memo submitted to the DAIDS PRO.

NOTE: If an amendment registration submission is missing any required documents or is incomplete, designated site personnel (i.e., CRS coordinator, IoR) and/or additional personnel listed in the DPRS will be sent a Materials Request notice that details the missing and/or corrected information/materials that must be submitted to the DAIDS PRO. For information on how to submit requested materials refer to Section VI, Sub Section C.iv.- "Requested Materials" of this manual.

A CRS will receive a Registration Notification from the DAIDS PRO that will include all languages and informed consent types that have been submitted. The Registration Notification from the DAIDS PRO indicates successful completion of the initial protocol registration process.

NOTE - A Registration Notification from the DAIDS PRO is NOT required prior to implementing an amendment at a CRS.

NOTE: Once a new version of a protocol is approved by DAIDS and has been distributed to the sites, a CRS will no longer be able to register for a previous version.

NOTE: If a CRS has submitted a registration packet for a previous version of a protocol prior to a new version being approved by DAIDS and distribution to the sites, the DAIDS PRO will continue to process the registration for the earlier version.

ii. Letter of Amendment (LoA) Registration

Per the DAIDS Protocol Registration policy, CRSs are required to submit a LoA and any amended site-specific informed consent form(s), to their IRB/EC for review and approval within 30 calendar days for U.S. sites and 60 calendar days for non-U.S. sites of the date the LoA was approved by DAIDS and distributed to the sites.

NOTE: The 30 or 60 calendar day requirement for submission of amendment materials is for local IRB/EC only.

NOTE: ICF revisions resulting from LoAs DO NOT affect the DAIDS protocol version. For version tracking purposes at the CRS (i.e., at the request of an IRB/EC and other applicable REs, CRSs can specify the site (local) version number or version date of the site-specific ICF(s) in the header or footer of their site-specific ICF(s). However, the DAIDS protocol version number should remain on all site-specific ICFs as well.

Once a CRS has received final approval from the IRB/EC and other applicable REs, the LoA and any revised site-specific ICF(s) must be implemented immediately. A CRS must submit LoA registration documents to the DAIDS PRO within 14 calendar days of a CRS's receipt of final IRB/EC approval for the LoA. The submitted documents must include documentation of the date the LoA and any revised site-specific ICF(s) were submitted to the IRB/EC.

The following documentation must be submitted to the DAIDS PRO for all LoA registration submissions:

- A copy of the site's IRB/EC and other applicable RE approval letter(s) and any other documentation/correspondence with the IRB/EC other applicable REs
- Documentation of the date the LoA and any revised site-specific ICF(s) were submitted to the IRB/EC
- A copy of the IRB/EC and other applicable RE approved site ICF(s) (all languages including English translations, if applicable)

NOTE: If the IRB/EC determines that an LoA does not require changes to the site-specific ICF(s), the CRS should document this either in the comments section of the ICF field of the DPRS or with a memo to the DAIDS PRO with the LoA registration submission.

A CRS will receive a Registration Notification from the DAIDS PRO for each LoA registration submission. The Registration Notification from the DAIDS PRO indicates successful completion of the LoA registration process.

NOTE - A Registration Notification from the DAIDS PRO is NOT required prior to implementing a LoA at a CRS.

C. OTHER SUBMISSIONS

Other submissions are *ANY* submissions made to the DAIDS PRO that are not an Initial, Amendment or LoA registrations. Below is detailed information on requirements related to "other submissions" a CRS may submit to the DAIDS PRO.

i. Disapprovals

If it is determined during the DAIDS PRO review process that a site-specific ICF(s) does not include all the required basic and appropriate additional elements to comply with U.S. federal regulations and DAIDS policies, designated CRS personnel (i.e., CRS Coordinator, IoR) will be notified via a Disapproval Notification from the DAIDS PRO regarding the deficiencies. The disapproval notification will outline the deficiencies in the site-specific ICF(s) that must be revised or corrected before a final Registration Notification can be issued.

Upon receipt of a Disapproval Notification from the DAIDS PRO a CRS has two options:

1. Make the necessary revisions/corrections and submit the revised document(s) to their IRB/EC for review and approval. Upon receiving final IRB/EC approval for the revised document(s) the CRS must resubmit the revised/corrected documents to the DAIDS PRO for review.

OR

2. Submit justification for the omission/changes to the DAIDS PRO via a request for Disapproval Reversal

Under Option 1 - The following documentation must be submitted to the DAIDS PRO once a CRS receives final IRB/EC and other applicable RE approval for the revised document(s):

- A copy of the IRB/EC and other applicable RE approval letter(s) for the revised document(s)
- A copy of the IRB/EC and other applicable RE approved revised site ICF(s)

When ALL required documents have been received and it is confirmed that the required revisions/corrections have been made, the DAIDS PRO will issue a Registration Notification.

Under Option 2 - If a CRS believes that a Disapproval Notification has been issued in error, the CRS can submit a request for Disapproval Reversal. A CRS

must provide justification and /or documentation explaining why the disapproval should be reversed.

The following documentation must be submitted to the DAIDS PRO to request a disapproval reversal:

- Written justification and/or a copy of any documentation supporting the CRS's request for the disapproval reversal

A CRS will be notified within 4 business working days as to whether or not the disapproval will be reversed via e-mail from the DAIDS PRO.

ii. Administrative Registration

Administrative registrations should occur when a site is not recruiting participants in a DAIDS-supported and/or sponsored clinical trial but has administrative functions only. Protocol/Grant Principal Investigator (PI) or Protocol Chair/Co-Chair's routinely make substantial study interventions (decisions and interpretations) that affect study participants even though participants may not be enrolled or seen at the Protocol/Grant Principal Investigator (PI) or Protocol Chair/Co-Chair's CRS. As a result, the Protocol/Grant Principal Investigator (PI) or Protocol Chair/Co-Chair's institutions are considered engaged with the research and must assure compliance with applicable HHS regulations. For more information on engagement refer to the OHRP guidance document found at the following website: http://www.hhs.gov/ohrp/humansubjects/guidance/engage08.html

Based on U.S. federal regulation[8&9], "each institution engaged" in human subjects research that is supported and/or sponsored by the Department of Health and Human Services (DHHS) must provide the OHRP with a satisfactory Assurance of Compliance with the regulations, unless the research is exempt under U.S. federal regulation[10].

For all administrative registrations, DAIDS requires that that the Protocol/Grant PI or Protocol Chair/Co-Chair consult with their IRB/EC and receive documentation in writing of the IRB/EC's decision concerning their IRB/EC's protocol review and approval. At least two different kinds of decisions can be made:

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[8] 45 CFR §46.103(a)
[9] http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm#46.103
[10] 45 CFR §46.101(b)

1) IRB/EC wants to be involved in reviewing and approving the protocol,

2) IRB/EC does not want to be involved in reviewing and approving the protocol and will rely on another IRB/EC, designated on the Federal Wide Assurance (FWA), for review and approval

DAIDS will honor the decision of the IRB/EC. The Protocol/Grant PI(s) or Protocol Chair/Co-Chair (s) need to consult with their IRB/EC and obtain written documentation of the IRB/EC's decision regarding their review and approval of the protocol in order to comply with U.S. federal regulations.

Upon receipt of final approval and/or documentation from the IRB/EC, an administrative registration submission should be made to the DAIDS PRO.

The following documentation must be submitted to the DAIDS PRO for all Administrative Registrations:

- A copy of the IRB/EC approval letter *AND* any other documentation from the IRB/EC including the IRB/EC decision regarding protocol review and approval
- A copy of the Form FDA 1572 signed and dated by the Protocol/Grant PI(s) or Protocol Chair/Co-Chair (for studies conducted under an IND)

OR

- A copy of the DAIDS IoR Agreement signed and dated by the Protocol Protocol/Grant PI(s) or Chair/Co-Chair (for non-IND studies)
- A copy of the Protocol/Grant PI(s) or Protocol Chair/Co-Chair CV

A CRS will receive a Registration Notification from the DAIDS PRO. The Registration Notification from the DAIDS PRO indicates successful completion of the administrative registration process.

iii. Change of Investigator of Record (IoR)

When there is a change in the IoR listed in item 1 on the Form FDA 1572 or DAIDS IoR Agreement, a CRS must submit a copy of the revised Form FDA 1572 or the revised DAIDS IoR Agreement to the DAIDS PRO. To officially change the IoR for a protocol(s), the CRS must submit the documentation within 30 calendar days of the CRS's notification that the current IoR will no longer serve as the IoR for the study.

The following documentation must be submitted to the DAIDS PRO for all Change of IoR requests:

- Memo requesting a change of IoR
- A copy of the new Form FDA 1572 signed and dated by the new IoR (for studies conducted under an IND)

OR

- A copy of the new DAIDS IoR Agreement signed and dated by the new IoR (for non-IND studies)
- CV for the new IoR

The DAIDS PRO will issue a decision for all Change of IoR submissions within 10 business days from the date of receipt of a complete packet.

A CRS will receive a final Change of IoR Approval Notification from the DAIDS PRO when the change of IoR has been approved by the DAIDS PRT.

NOTE: The Change of IoR is NOT official until the CRS receives a Change of IoR Approval Notification from the DAIDS PRO.

NOTE: A CRS must notify their DAIDS Office for Clinical Site Oversight (OCSO), representative and/or DAIDS Program Officer when there is a change in CRS Leader or other CRS site personnel and/or contact information.

iv. Requested Materials

Requested materials are additional and/or corrected materials requested by the DAIDS PRO as a result of an incomplete submission to the DAIDS PRO. If any required documents are missing, incomplete, or are inaccurate, the DAIDS PRO will issue a Materials Request notice to designated CRS personnel (i.e. CRS Coordinator, IoR). This request *will* stop the registration review process.

NOTE: The Protocol Registration review process will not continue until all Requested Materials have been received by the DAIDS PRO.

The following documentation must be submitted to the DAIDS PRO in response to a Materials Request Notification:

- A copy of the requested materials

CRSs will receive a Confirmation of Submission notice once the requested materials have been received by the DAIDS PRO.

v. Continuing/Annual Review

The HHS regulations[11] require that all HHS supported research undergo continuing IRB/EC review at intervals appropriate to the degree of risk, but NOT LESS than once per year. Continuing review should be performed prior to the expiration date specified on the IRB/EC approval letter(s) and/or site-specific ICFs. The frequency of ongoing reviews should be documented in IRB/EC policies and procedures and may be protocol/study specific. CRSs can visit the OHRP website for additional guidance related to continuing review.

CRSs participating in DAIDS-supported and/or sponsored clinical trials are required to submit documentation of IRB/EC Continuing/Annual review approval to the DAIDS PRO. Continuing/Annual review documentation must be submitted to the DAIDS PRO within 14 days of the CRS receiving final IRB/EC Continuing/Annual review approval documentation. The IRB/EC approval of continuing review must be a final approval and not require any modifications or further input by the CRS, and the site-specific ICFs are approved for use as written.

The following documents must be submitted to the DAIDS PRO for all continuing/annual review submissions:

- A copy of the IRB/EC Continuing/Annual review approval letter *AND* any other documentation from the IRB/EC
- A copy of the IRB/EC approved site ICF(s) if revised at the time of Continuing/Annual review

NOTE - All IRB/EC approval letters for Continuing/Annual review must state that the approval is for continuing review (i.e., similar terminology is acceptable: yearly review, annual review etc.)

NOTE: Documentation of IRB/EC receipt of continuing review request alone does not satisfy the DAIDS requirement regarding documentation of Continuing/Annual review and approval by the IRB/EC.

CRSs will be sent a Confirmation of Submission notice that indicates materials have been received by the DAIDS PRO. CRSs will *NOT* receive any additional notifications from the DAIDS PRO for Continuing/Annual review documentation.

[11] 45 CFR §46.109(e)

If a CRS's IRB/EC procedures for expedited review deviate from those as specified in OHRP guidance (i.e., specific pre-approved country procedures), then the CRS must provide documentation of the IRB/EC procedures to the DAIDS PRO at the same time the CRS submits their IRB/EC Continuing/Annual review approval documents. In addition, documentation of any change in timing of the IRB/EC review procedure for Continuing /Annual reviews for the CRS must be submitted to the DAIDS PRO along with the final IRB/EC Continuing/Annual review approval letter(s).

Lapses in Continuing Review

Per the HHS regulations[12] as and OHRP guidance on continuing review[13], if there is a lapse in continuing review (e.g., if an investigator has failed to provide continuing review information to their IRB/EC or the IRB/EC has not reviewed and approved a research study by the Continuing/Annual review date specified by the IRB/EC), the research at the CRS must stop, unless the IRB/EC finds that it is in the best interest of individual participants to continue participating in the research interventions or interaction. Enrollment of new participants cannot occur after the expiration of IRB/EC approval(s).

CRSs should contact their DAIDS Office for Clinical Site Oversight (OCSO) representative (NIAIDOCSO@niaid.nih.gov) and/or DAIDS Program Officer along with the DAIDS Human Subjects Protection Branch (HSPB) (NIAIDDAIDSHSPB@niaid.nih.gov) for additional guidance and information.

vi. Site Initiated Revisions to Site Informed Consent Forms (ICFs)

Modifications to a CRS's site-specific ICFs are considered site initiated when the changes are made as a result of new information or at the request of the IRB/EC and other applicable REs.

Revisions to a CRS's site-specific ICFs are only considered site initiated when revisions have been made after the CRS has received a Registration Notification from the DAIDS PRO for the most current DAIDS-approved protocol version. Any changes made to a CRS's ICF(s) prior to receiving a Registration Notification from the DAIDS will be considered part of the CRS's initial or amendment registration. For additional information on initial and amendment registration submissions refer to Section VI, Sub-Sections A - "Initial Registration" and B - "Amendment Registration" of this manual.

Site-initiated revisions *DO NOT* affect the final DAIDS protocol version number and CRSs must be sure that the correct DAIDS protocol version number,

[12] 45 CFR §46.103(b) & §46.109(e)
[13] http://www.hhs.gov/ohrp/humansubjects/guidance/contrev0107.htm

remains on all site ICF(s). For version tracking purposes at the CRS (i.e., at the request of an IRB/EC and other applicable REs), CRSs can specify the site (local) version number or version date of the site-specific ICF(s) in the header or footer of their site-specific ICF(s). However, the final DAIDS protocol version number should remain on all site-specific ICFs as well.

The following documentation must be submitted to the DAIDS PRO for all site-initiated revised ICFs:

- A copy of the site initiated revised ICF(s)
- A copy of the IRB/EC and other applicable RE approval letter(s)

Once the CRS receives approval from their IRB/EC and other applicable REs, the CRS may implement the revised site ICFs immediately. The DAIDS PRO will not review the site initiated revisions to CRS's ICFs.

CRSs will be sent a Confirmation of Submission notice that indicates materials have been received by the DAIDS PRO. CRSs will *NOT* receive any additional notifications from the DAIDS PRO for site initiated revisions to site-specific ICFs.

vii. Updated Form FDA 1572 or DAIDS Investigator of Record (IoR) Agreement

When there is *ANY* change to the information listed on the Form FDA 1572/DAIDS IoR Agreement originally submitted to the DAIDS PRO, a CRS must submit an updated Form FDA 1572 (IND studies) or DAIDS IoR Agreement (Non-IND studies).

Any correction or revision requires the IoR to sign and date the newly revised form even if the change(s) only affects one page of the form. A CRS must submit a copy of BOTH pages (and supplemental page, if applicable) of the revised Form FDA 1572 or the entire revised DAIDS IoR Agreement to the DAIDS PRO.

The following documentation must be submitted to the DAIDS PRO for all Updated Form FDA 1572s/DAIDS IoR Agreements:

- A copy of the updated Form FDA 1572 signed and dated by the IoR (for studies conducted under an IND)

OR

- A copy of the updated DAIDS IoR Agreement signed and dated by the IoR (for non-IND studies)

NOTE: If there is a Change of IoR (listed in Item #1 of either form), refer to Section VI, Sub-Section C.iii - "Change of Investigator of Record" of this manual.

NOTE: CRSs must submit a copy of the signed and dated Form FDA 1572/DAIDS IoR Agreement to the DAIDS PRO and retain the original version in their regulatory files at the site.

CRSs will *NOT* receive a Registration Notification from the DAIDS PRO for Updated Form FDA 1572s or DAIDS IoR Agreements unless the updated document(s) results in a Change of IoR at the CRS.

viii. Deregistration

Any CRS that has completed the DAIDS protocol registration process for a protocol (main or sub-study), must complete the DAIDS deregistration process for each protocol to which it is registered

NOTE: Deregistration is NOT automatic when a study is completed.

Deregistration can occur when:

- The CRS no longer has participants on study (all follow-up has been completed) and does not plan to enroll additional subjects
- If no participants were ever enrolled at the CRS and the study has closed to accrual.

The DAIDS deregistration process is independent of a CRS's closure/termination of a study at their IRB/EC. The IRB/EC's determination to close or terminate a study is *NOT* required for a CRS to deregister with DAIDS. Completion of the DAIDS deregistration process indicates that a CRS's participation in a study is complete but does not reflect the closure of a multi-center study at all CRSs participating in the study.

If a CRS plans to complete the DAIDS deregistration process for a study but will not be closing/terminating the study at their IRB/EC, the CRS should consult its IRB/EC to confirm any requirements and/or standard operating procedures that must be met prior to deregistration. A CRS's IRB/EC may require the continued submission of safety information and/or other data for the study. In this case, deregistration with DAIDS PRO should *NOT* be done until the study has been completed at all participating sites.

In addition, a CRS should contact their DAIDS Clinical Trials Network or DAIDS Program Officer to confirm any protocol, network and/or DAIDS specific requirements prior to deregistering with the DAIDS PRO and/or closing/terminating the study with the IRB/EC.

The following documentation must be submitted to the DAIDS PRO for all deregistration requests:

- Memo stating that the CRS no longer intends to participate in the protocol(s)

AND/OR

- A Copy of the IRB/EC closure/termination letter for the protocol

The DAIDS PRO will issue a decision for all deregistration submissions within 10 business days from the date of receipt of a complete packet. Once a CRS receives a Deregistration Notification from the DAIDS PRO for a protocol, the CRS is no longer required to submit any additional protocol registration documents to the DAIDS PRO if the protocol amends. A CRS must continue to follow their IRB/EC requirements for submission of documents if the protocol has not been closed/terminated with the IRB/EC.

NOTE: A CRS is not considered deregistered until a Deregistration Notification has been issued by the DAIDS PRO.

Upon completion of the DAIDS deregistration process, a CRS will no longer receive safety information (e.g. safety reports, safety memos, investigator's brochures, etc.) from the DAIDS RSC Safety Information Center.

VIII. APPENDIX A - INSTRUCTIONS ON HOW TO SUBMIT PROTOCOL REGISTRATION MATERIALS THROUGH THE DPRS

Below is information on how to submit protocol registration materials through the DPRS once a User Name and Password has been assigned:

1. Go to https://daidses.niaid.nih.gov/ProtocolRegistration
2. Enter your User Name and Password and click *Login*.
3. From the *Home* page, click *New Submission* in the main navigation bar.
4. *Enter the Submission Details*: Enter the appropriate information under the *Site & Protocol details* heading. Click the icon to select the Site, IoR and Protocol Number. Click the drop down box to select the version.
5. *Submissions*: Select the appropriate checkboxes under the *Submissions* heading.
6. *Save***:** Click *Save*. If the save is successful, the *Upload Documents* heading will appear in the lower half of the screen.
7. *Upload Documents***:** Click the icon to upload the appropriate documents. Enter notes to provide additional clarification. Click *Submit*.
8. *Confirm Submission Details***:** Confirm the Site, and Protocol Number. Select the version and click *Submit*.
9. You will receive an e-mail to confirm that the submission was successful.

More information on the DPRS and how to request a User name and Password is available at http://rcc.tech-res.com/prs/default.html.